Supplementary material:

Macaque handling:

In studies 1A and 1B, cynomolgus macaques (*Macaca fascicularis*) from China were provided by Charles River Laboratories Japan, Inc., and were quarantined and acclimated for 6 weeks or more at the test facility. Macaques were kept in individual cages, with temperature range of 24 – 27 °C and lightening period of 12 hours per day. Diet (pellets, high calorie liquid and fruit) was given daily, water was delivered throughout the day with automatic system. Macaques were assigned to the test groups three days before initial dosing by weight-stratified randomization.

In studies 2A and 2B, cynomolgus macaques (*Macaca fascicularis*) from Mauritius were provided by LCL-Cynologics (Port-Louis, Mauritius), and were quarantined and acclimated for 1 weeks at the test facility. Macaques were kept in individual cages, with temperature range of 23 – 24°C and lightening period of 12 hours per day in study 2A and 14.5 hours per day in study 2B. Diet (pellets, fruit) was given daily, water was available throughout the day. Macaques were assigned to the test groups using body weights before initial dosing by weight-stratified randomization.

Safety:

Several adverse events were reported consecutively to favipiravir administration in the four studies, yet none of them was considered as serious abnormality. Vomiting was the most common, systematically occurred within 4 days after treatment initiation, and was reported once in 3 animals in study 1A, once in 5 animals in study 1B, once in one animal in study 2A and once to thrice in 5 animals in study 2B. Transient absence of stool lasting 1 or 2 days, excepted for one animal (4 days), was observed in 3 animals in study 1B and 6 animals in study 2B. Stereotypies, described as intermittent backward head movements, were reported only in studies 2A and 2B, respectively in one and two animals.

Food consumption had large intra and inter individual variability along the studies (Figure A1). Transient decrease of food consumption was observed in the four studies within the 3 days after treatment initiation, followed with clear rebound, excepted in the study 1B group receiving 150 mg/kg BID. In this last group, food intake remains irregular after D3. After premature dosing interruption, food intake quickly increased in 3 of 4 monkeys.

Median loss of weight along the experimentation were 0.10, 0.30, 0.32 and 0.27 kg in studies 1A, 1B, 2A and 2B respectively. No significant difference was found between the studies (Kruskal-Wallis test, $p=0.54$), the levels of maintenance dose (Kruskal-Wallis test, $p=0.87$) and the duration of the study (Wilcoxon test, $p=0.73$).

Median drop of hemoglobin blood level was found to 2.3, 2.3, 2 and 1.3 g/dL respectively in studies 1A, 1B, 2A and 2B. No significant difference was found between the studies (Kruskal-Wallis test, $p=0.75$), the levels of maintenance dose (Kruskal-Wallis test, $p=0.75$) and the duration of the study (Wilcoxon test, $p=0.12$).

Considering blood chemistry parameters, moderate increase of ALT activity, biomarker of hepatocyte cytolysis was observed in the four studies, to 38, 25, 32 and 26 IU/L. No significant difference was found between the studies (Kruskal-Wallis test, p=0.16), the levels of maintenance dose (Kruskal-Wallis test, p=0.68) and the duration of the study (Wilcoxon test, p=0.21). Plasma creatinine, biomarker of renal function, had a median increase of 18.3 µmol/L in study 2A, whereas decrease was found in study 1A (-16.8 µmol/L). Changes were low in studies 1B and 2B, +8.8 and +1.5 µmol/L respectively. These interstudies discrepancies were statically significant (Kruskal-Wallis test, p=0.003). Study duration effect was found significant (Wilcoxon test, p=0.013), pointing out a possible time related impact of favipiravir administration on renal function. Yet, the clinical impact of the observed increase remains moderate, and the statistical effect is strengthened by the creatinine decrease in study 1A. No other clinically relevant changes of blood chemistry parameters were reported.

No abnormalities were noticed in animal necropsies in studies 1B, 2A and 2B.

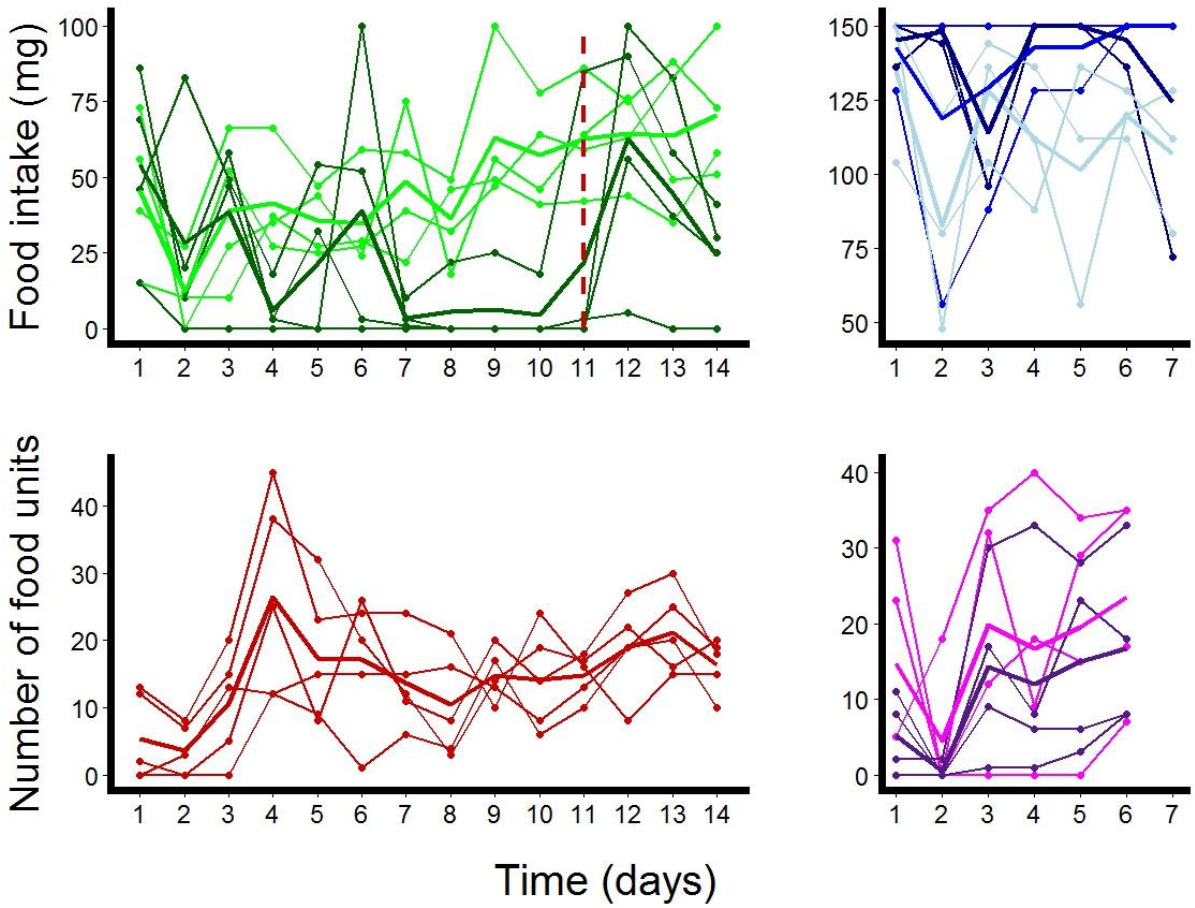


Figure A1: Food consumption evolution over study periods. Top left study 1B, light green lines 100 mg/kg group, dark green lines 150 mg/kg group, vertical red dashed line dosing interruption for 150 mg/kg. Top right study 1A, light blue lines 60 mg/kg group, blue lines 100 mg/kg group,

dark blue lines 150 mg/kg group. Bottom left study 2A, red lines 100 mg/kg group. Bottom right study 2B, magenta lines 150 mg/kg group, purple lines 180 mg/kg group. Bold solid line in each plot represent group median.

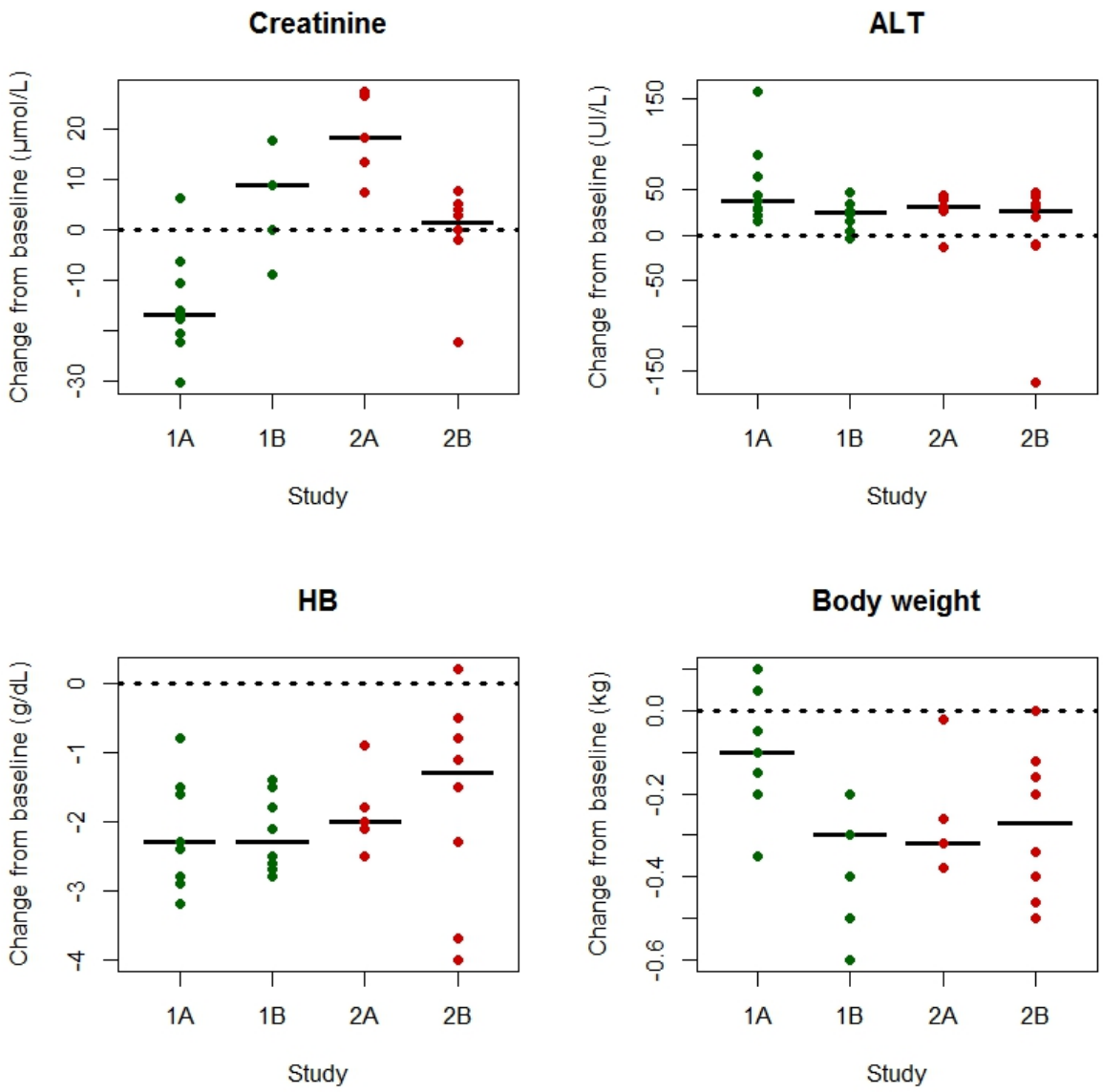


Figure A2: Clinical and biological parameters changes from baseline to end of studies. Green Chinese cynomolgus macaques, red Mauritian cynomolgus macaques.

Non compartmental analysis of favipiravir concentrations:

The maximal concentrations, C_{max} was measured 5 min after the end of the infusion and the residual concentrations, C_{trough}, was measured just before the beginning of the second infusion of the day. We considered steady state was reached at day 6. The terminal half-lives (HL) were approximated by linear regression of logarithm concentrations of the 3 final points before new administration. Areas under curve (AUC) were computed using trapezoidal method with natural concentrations. We computed $AUC_{0\text{-}12h}$ for the first dose on day 1 and last doses on day 7-14, and AUC extrapolated to infinity (AUC_{inf}) on day 1, equal to $AUC_{012} + \frac{HL \times C_{12h}}{\ln(2)}$. The average concentrations, C_{ave}, were calculated as $AUC_{0\text{-}12h}/12$. Non compartmental clearance, CL, on day 1 and days 7-14 were calculated as $CL = Dose/AUC_{inf}$ and $CL = Dose/AUC_{0\text{-}12h}$, respectively. Data below the limit of quantification were set at the limit of quantification value for the non-compartmental analysis. The analysis was performed using R software version 3.1.2.

Analysis Methods and cross validation of favipiravir concentration assay:

Methods:

Blood samples of 0.8-1.5 mL were collected in cynomolgus macaques on EDTA K2 tubes for each time point, and centrifuged in the hour following the sampling.

Analytical methods for Japanese and French studies were performed separately. Favipiravir plasma concentrations from studies 1 were assayed using reference method developed by Toyama Chemicals, Japan, called method A below, consisting in high performance liquid chromatography (HPLC) associated to UV detection (Shimadzu 10A coupled to SPD-10A, Shimadzu Corporation). The limit of quantitation of the method was 0.1 mg/L. Samples from studies 2 were assayed by Eurofin/ADME Bioanalyses, Strasbourg, France, using HPLC (Kromasil C18) coupled to tandem mass spectrometry detection (API4000), designed as method B, with a limit of quantitation of 5 mg/L.

In order to allow comparison of Chinese and Mauritian cynomolgus macaques, assessment of reproducibility of favipiravir plasma concentration analytical process was evaluated in a cross validation study. Fifteen samples of cynomolgus macaques from study 2A, 9 peaks and 6 residuals, were blindly assayed by the two laboratories. Assessment of the agreement of the two analytical processes was performed using method B concentrations vs method A concentrations

plot, differences against method A concentrations plot, and computing absolute error and relative error for each sample, as:

Error = Method B concentration – Method A concentration

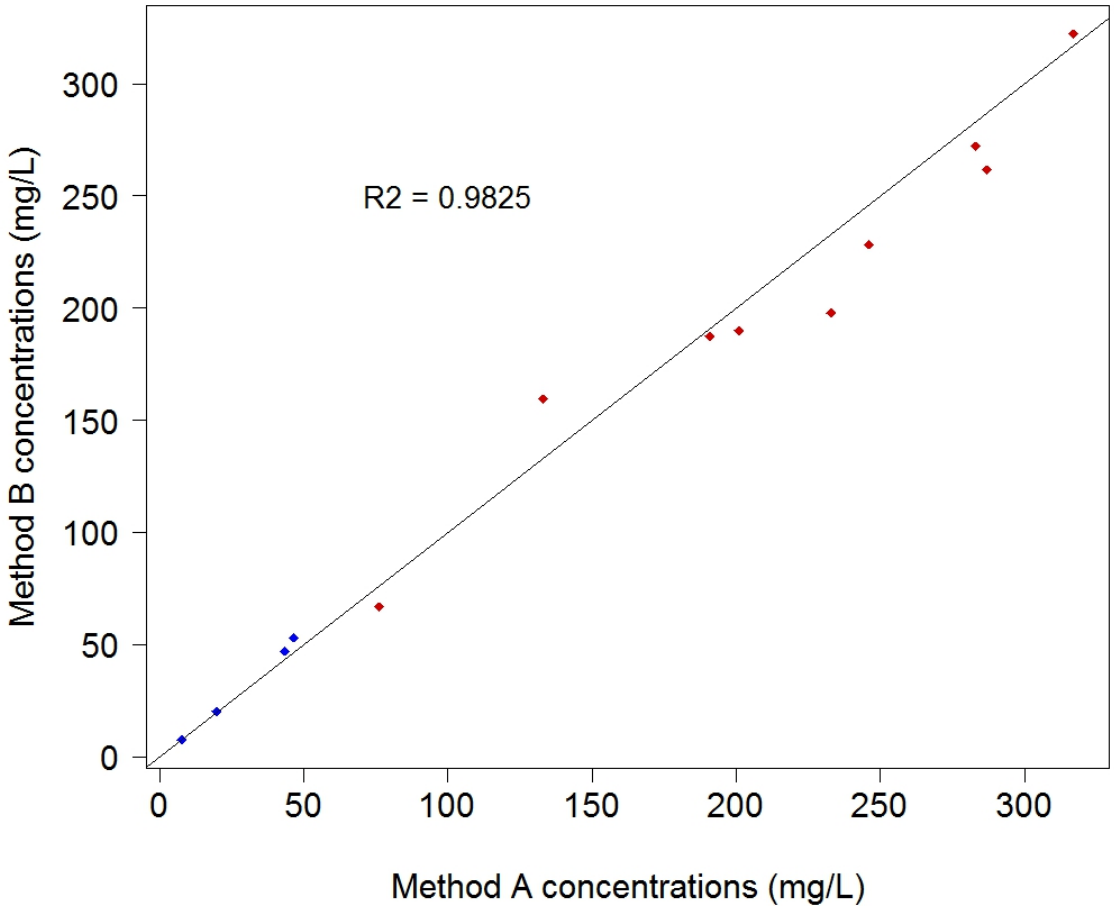
Relative error = (Method B concentration – Method A concentration)/ Method A concentration

Mean, median, maximum, minimum and standard deviation of errors and relative errors were calculated. Bias and relative bias were defined as mean of error and relative error, respectively. Data below the limit of quantitation (LOQ) of Reaction's analytical process (5 mg/L) were excluded from the analysis and reported separately.

Results:

N=13	error (mg/L)	relative error
mean	-5.48	-1.1%
sd	15.59	10.1%
min	-35.16	-15.1%
max	26.35	19.8%
median	-3.60	-3.9%

Agreement between the two assays was stated by the cross validation study. Method B slightly under-predicts peak concentrations of favipiravir, and over predicts residual concentrations (Figures A3 and A4). However, only two absolute relative errors were higher than 15%, one is positive and the second negative, and the relative bias was computed to -1.1%, so is quite low. Two residual concentrations were found under the LOQ (5 mg/L) by method B, and these samples were assayed to 2.22 and 2.62 mg/L by method A, showing good agreement for the lowest concentrations.



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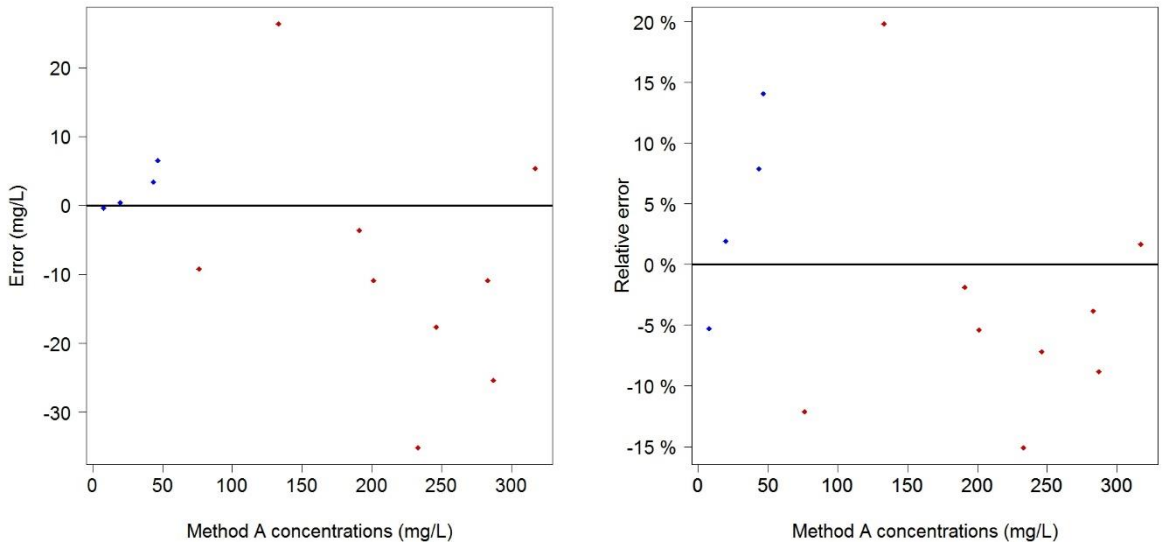
116 Figure A3: Favipiravir natural concentrations assayed by method B plotted vs ones assayed by
117 method A. Red dots are peak concentrations, blue ones are residual concentrations.



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119 Figure A4: Error and relative errors of favipiravir concentrations plotted versus method A
120 concentrations. Red dots are peak concentrations, blue ones are residual concentrations.

Favipiravir *in vitro* EC_{50} assessment for Marburg virus

Because it was not reported in the literature, an experiment was performed to determine the EC_{50} of favipiravir against Marburg virus in the biosafety level 4 (BSL-4) laboratory at the Bernhard Nocht Institute for Tropical Medicine in Hamburg. Methodology was previously described in (12, 13). In brief, Vero E6 cells (4×10^4 cells per well) were inoculated with MARV strain Leiden (2) with a multiplicity of infection of 0.01 and drug was added 1 h post infection. Concentration in cell culture supernatant of infectious virus particles was measured 5 days post infection by real time PCR. The concentrations that reduced the virus titer by 50% and 90% (EC_{50} and EC_{90}, respectively) were calculated from dose– response curves by nonlinear regression.

Table A1: Model prediction of favipiravir plasmatic total concentration profiles in female Chinese and Mauritian cynomolgus, on day 1, day 7 and day 14 after treatment initiation. Five thousand individual profiles were simulated for each scenario, and median, 5th and 95th percentiles were reported.

Origin	Dosing (mg/kg BID)			C_{trough}(mg/L)			C_{max} (mg/L)			C_{ave} (mg/L)		
	D1	D2-D7	D8-D14	D1	D7	D14	D1	D7	D14	D1	D7	D14
Mauritian	200	60	60	0.0 [0.0-43.0]	0.0 [0.0 - 3.6]	0.0 [0.0 - 0.6]	413.0 [308.8 - 531.8]	142.4 [107.0 - 183.2]	136.0 [101.6 - 176.4]	30.6 [13.6 - 136.8]	12.8 [5.4 - 46.8]	9.0 [4.2 - 31.8]
Mauritian	100	100	100	0.0 [0.0-0.0]	3.4 [0.0 - 72.6]	0.0 [0.0 - 50.0]	200.8 [154.8 - 247.8]	265.4 [193.4 - 374.8]	246.4 [182.6 - 345.8]	9.8 [6.0 - 16.8]	67.2 [12.6 - 184.6]	33.0 [0.0 - 157.0]
Mauritian	200	100	100	0.0 [0.0 - 43.0]	3.0 [0.0 - 71.6]	0.0 [0.0 - 49.8]	413.0 [308.8 - 531.8]	264.2 [194.2 - 371.8]	246.4 [0.0 - 345.8]	30.6 [13.6 - 136.8]	67.6 [13.2 - 184.8]	33.0 [8.2 - 157.0]
Mauritian	200	100	120	0.0 [0.0 - 43.0]	3.0 [0.0 - 71.6]	1.6 [0.0 - 97.8]	413.0 [308.8 - 531.8]	264.2 [194.2 - 371.8]	306.8 [227.4 - 479.0]	30.6 [13.6 - 136.8]	67.6 [13.2 - 184.8]	59.8 [11.0 - 244.0]
Mauritian	200	100	150	0.0 [0.0 - 43.0]	3.0 [0.0 - 71.6]	15.6 [0.0 - 199.0]	413.0 [308.8 - 531.8]	264.2 [194.2 - 371.8]	406.8 [291.2 - 689.8]	30.6 [13.6 - 136.8]	67.6 [13.2 - 184.8]	125.0 [15.2 - 393.6]
Mauritian	250	130	130	0.2 [0.0 - 102.6]	31.0 [0.0 - 165.8]	4.6 [0.0 - 127.4]	520.4 [389.6 - 670.4]	379.0 [265.2 - 559.8]	339.0 [245.0 - 518.2]	53.4 [19.0 - 237.2]	149.2 [25.6 - 330.2]	81.8 [12.2 - 287.2]
Mauritian	150	150	150	0.0 [0.0 - 0.2]	60.2 [0.0 - 225.3]	16.8 [0.0 - 188.8]	304.0 [233.8 - 375.2]	459.3 [317.8 - 686.7]	408.8 [287.6 - 640.8]	17.2 [9.8 - 33.8]	215.0 [39.3 - 423.0]	132.0 [15.2 - 380.4]
Mauritian	250	150	150	0.2 [0.0 - 102.6]	60.6 [0.0 - 225.4]	16.8 [0.0 - 188.8]	520.4 [389.6 - 670.4]	459.6 [318.0 - 689.0]	408.8 [287.6 - 641.0]	53.4 [19.0 - 237.2]	215.0 [39.4 - 423.2]	132.0 [15.2 - 380.4]
Mauritian	250	150	180	0.2 [0.0 - 102.6]	60.6 [0.0 - 225.4]	52.0 [0.0 - 275.6]	520.4 [389.6 - 670.4]	459.6 [318.0 - 689.0]	523.0 [353.2 - 841.0]	53.4 [19.0 - 237.2]	215.0 [39.4 - 423.2]	219.8 [20.0 - 524.0]
Mauritian	250	180	180	0.2 [0.0 - 102.6]	117.8 [0.6 - 318.0]	52.2 [0.0 - 275.6]	520.4 [389.6 - 670.4]	597.8 [395.6 - 878.6]	523.0 [353.2 - 841.0]	53.4 [19.0 - 237.2]	312.2 [76.0 - 571.0]	219.8 [20.0 - 524.0]
Chinese	200	60	60	4.0 [0.0 - 88.2]	1.2 [0.0 - 26.8]	0.2 [0.0 - 14.8]	482.6 [375.6 - 605.0]	160.0 [121.0 - 208.6]	154.4 [118.4 - 197.8]	76.4 [33.4 - 205.8]	33.4 [13.2 - 88.4]	23.0 [9.8 - 71.2]
Chinese	100	100	100	0.0 [0.0 - 0.8]	33.4 [0.2 - 130.4]	9.4 [0.0 - 107.2]	237.4 [185.6 - 289.4]	302.2 [216.2 - 434.8]	277.8 [206.4 - 407.2]	22.8 [13.8 - 38.6]	123.8 [33.4 - 254.0]	78.8 [20.2 - 226.0]
Chinese	200	100	100	4.0 [0.0 - 88.2]	34.4 [0.2 - 131.8]	9.4 [0.0 - 107.4]	482.6 [375.6 - 605.0]	302.6 [216.2 - 435.0]	277.8 [206.4 - 407.2]	76.4 [33.4 - 205.8]	124.0 [34.0 - 255.6]	78.8 [20.2 - 226.0]
Chinese	200	100	120	4.0 [0.0 - 88.2]	34.4 [0.2 - 131.8]	24.6 [0.0 - 175.6]	482.6 [375.6 - 605.0]	302.6 [216.2 - 435.0]	347.2 [263.2 - 558.6]	76.4 [33.4 - 205.8]	124.0 [34.0 - 255.6]	119.2 [26.2 - 324.4]
Chinese	200	100	150	4.0 [0.0 - 88.2]	34.4 [0.2 - 131.8]	63.2 [0.0 - 296.2]	482.6 [375.6 - 605.0]	302.6 [216.2 - 435.0]	466.6 [340.0 - 753.2]	76.4 [33.4 - 205.8]	124.0 [34.0 - 255.6]	211.2 [37.8 - 475.6]

Chinese	250	130	130	21.2 [0.0 - 158.6]	86.8 [2.8 - 223.4]	39.2 [0.0 - 188.8]	604.4 [470.0 - 758.6]	434.0 [300.6 - 628.6]	387.4 [280.0 - 597.4]	128.2 [48.0 - 306.2]	216.0 [64.4 - 394.4]	152.4 [28.8 - 368.4]
Chinese	150	150	150	0.2 [0.0 - 9.2]	123.4 [8.6 - 289.4]	67.2 [0.0 - 255.8]	356.8 [278.8 - 435.4]	527.2 [359.2 - 756.6]	464.4 [327.8 - 718.8]	41.4 [23.0 - 78.4]	284.0 [93.2 - 493.2]	214.2 [38.0 - 455.4]
Chinese	250	150	150	21.2 [0.0 - 158.6]	123.6 [8.8 - 290.2]	67.2 [0.0 - 255.8]	604.4 [470.0 - 758.6]	527.4 [359.4 - 758.6]	464.4 [328.0 - 719.0]	128.2 [48.0 - 306.2]	284.2 [93.4 - 493.4]	214.2 [38.0 - 455.4]
Chinese	250	150	180	21.2 [0.0 - 158.6]	123.6 [8.8 - 290.2]	119.4 [0.0 - 360.8]	604.4 [470.0 - 758.6]	527.4 [359.4 - 758.6]	593.6 [405.0 - 904.8]	128.2 [48.0 - 306.2]	284.2 [93.4 - 493.4]	305.4 [50.2 - 598.8]
Chinese	250	180	180	21.2 [0.0 - 158.6]	187.6 [21.0 - 396.4]	119.4 [0.0 - 360.8]	604.4 [470.0 - 758.6]	670.6 [454.4 - 958.2]	593.6 [405.0 - 904.8]	128.2 [48.0 - 306.2]	383.6 [145.6 - 639.0]	305.4 [50.4 - 598.8]

Table A2: Proportions of macaques with predicted plasmatic free trough concentration below the HF viruses EC50s, on day 1, day 7 and day 14 after treatment initiation. Five thousand individual profiles were simulated for each scenario.

Origin	**Dosing (mg/kg BID)**		**CCHFV, JUNV**			**LAV**			**EBOV**		
	D1	**D2-D14**	**D1**	**D7**	**D14**	**D1**	**D7**	**D14**	**D1**	**D7**	**D14**
Mauritian	250	150	67.7%	12.1%	36.2%	88.9%	26.6%	51.1%	99.4%	67.3%	82.1%
Mauritian	250	180	67.7%	6.0%	25.1%	88.9%	14.6%	39.2%	99.4%	42.4%	65.2%
Chinese	200	100	44.3%	12.0%	35.0%	80.7%	37.7%	60.8%	99.6%	89.7%	94.2%
Chinese	250	150	19.7%	2.6%	14.9%	51.5%	9.5%	28.3%	94.9%	40.3%	61.8%

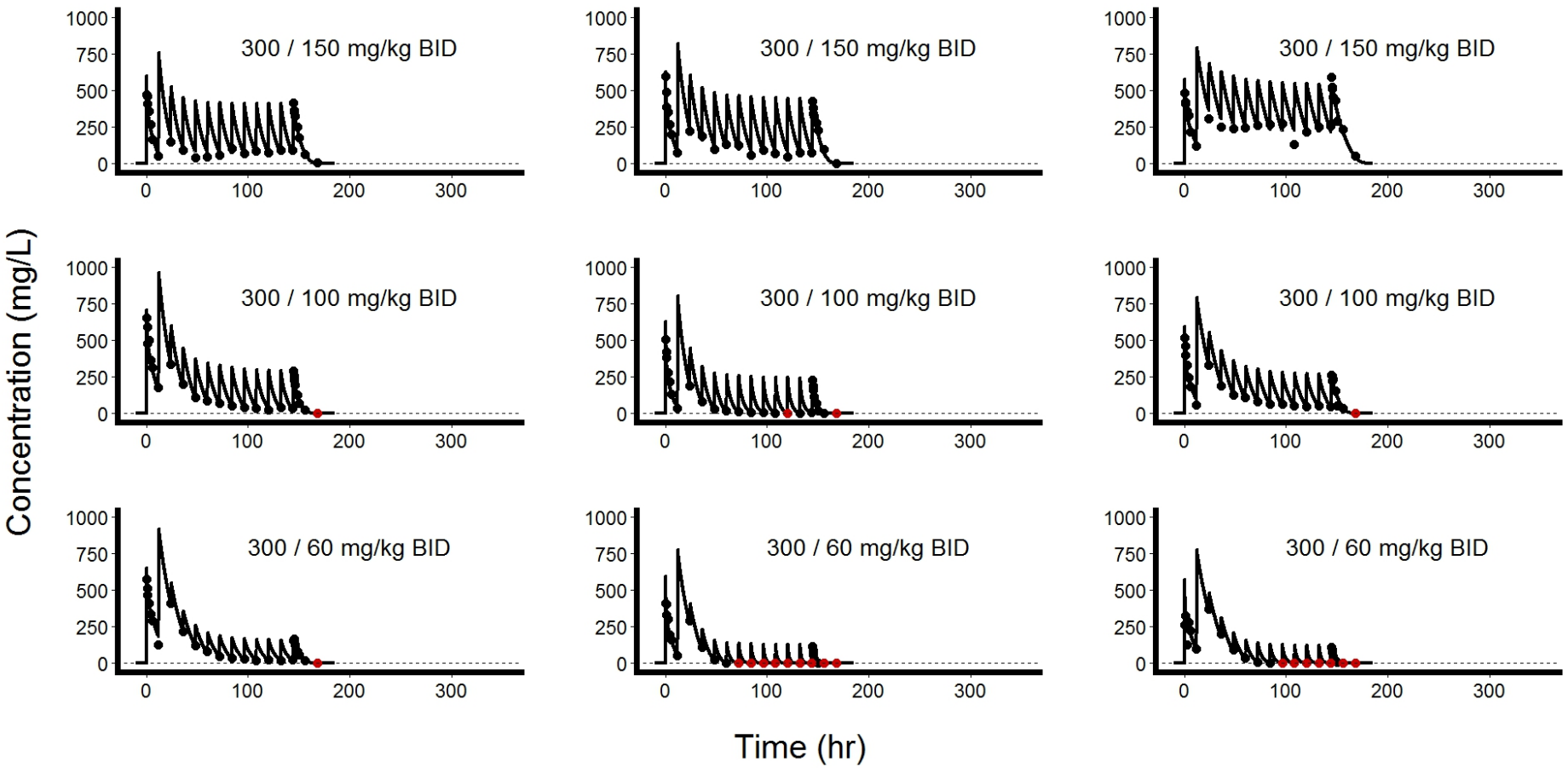

Concentration (mg/L)
300 / 150 mg/kg BID
300 / 100 mg/kg BID
300 / 60 mg/kg BID
1000
750
500
250
0
0
100
200
300
Time (hr)

Figure A5A

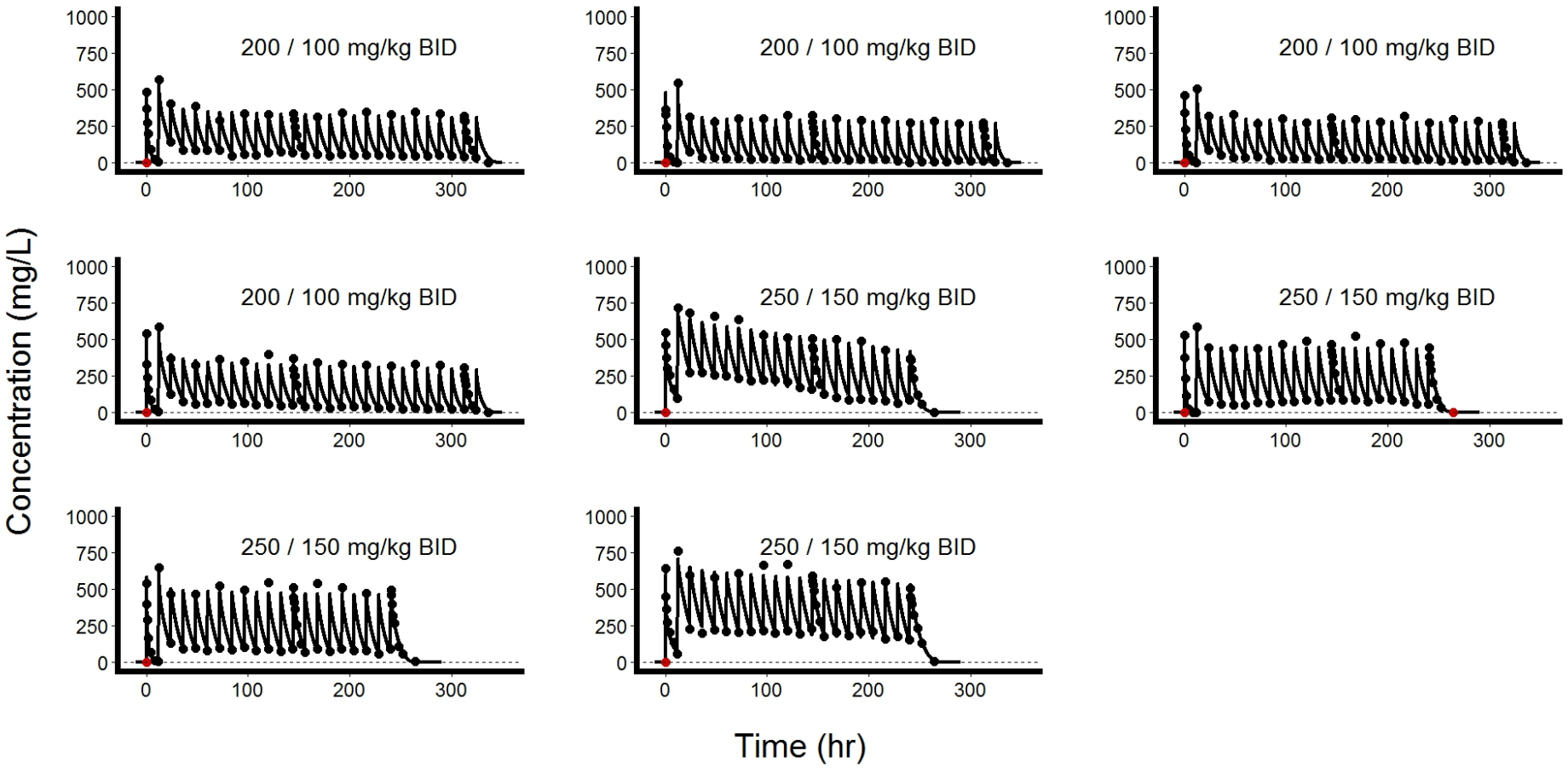

Concentration (mg/L)
200 / 100 mg/kg BID
200 / 100 mg/kg BID
200 / 100 mg/kg BID
200 / 100 mg/kg BID
250 / 150 mg/kg BID
250 / 150 mg/kg BID
250 / 150 mg/kg BID
250 / 150 mg/kg BID
1000
750
500
250
0
0
100
200
300
Time (hr)

Figure A5B

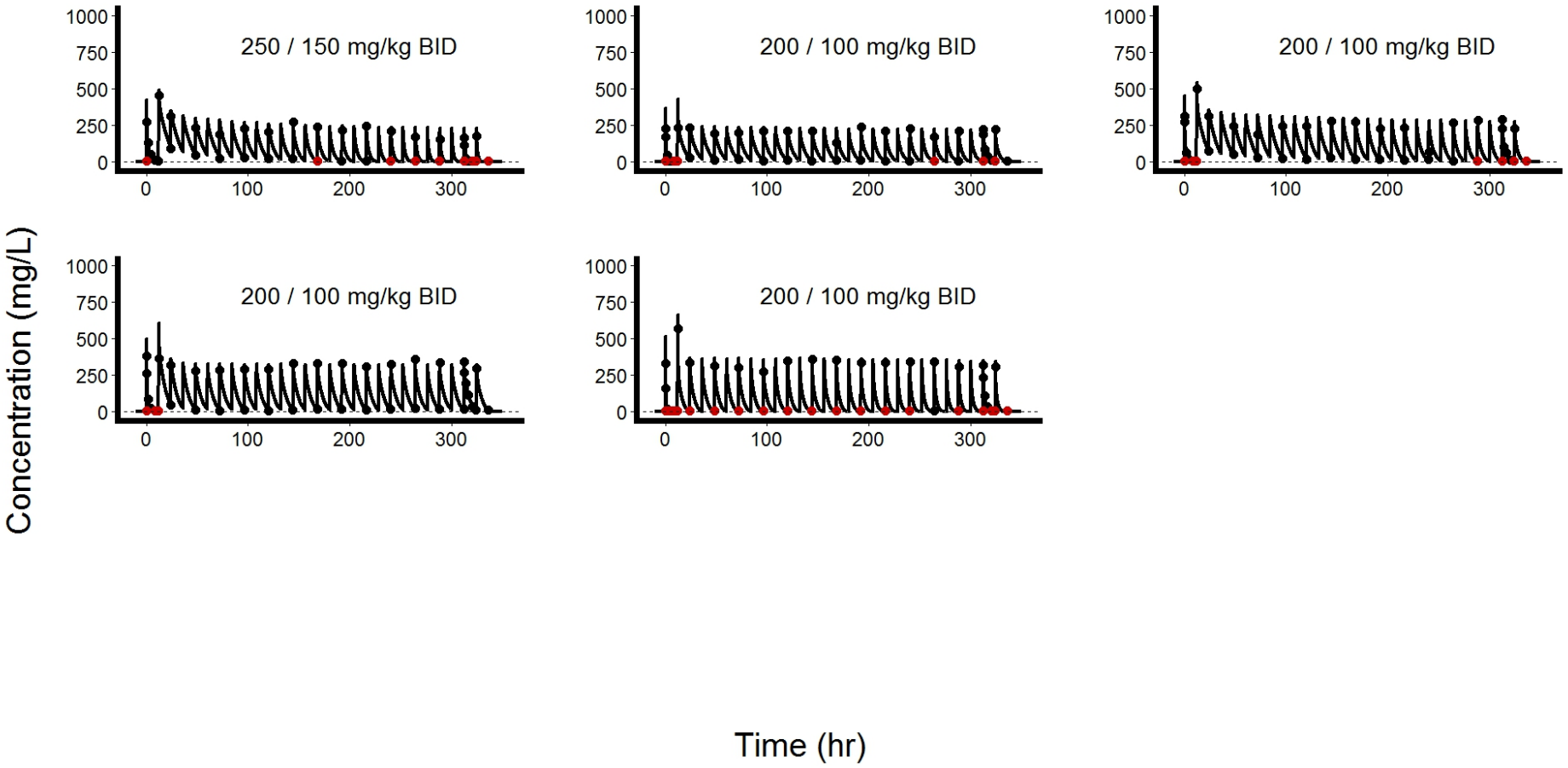
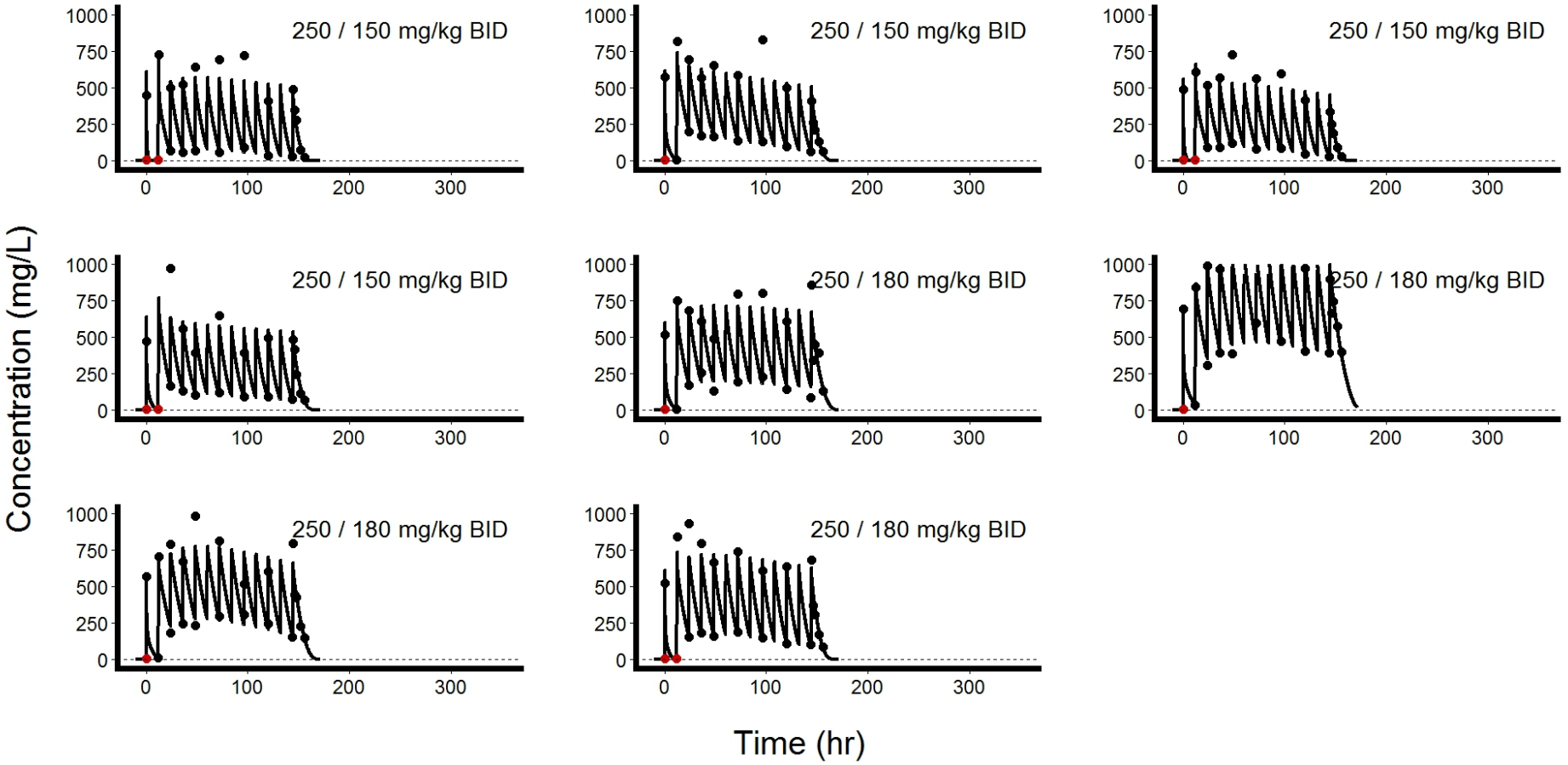

250 / 150 mg/kg BID
200 / 100 mg/kg BID
200 / 100 mg/kg BID
200 / 100 mg/kg BID
200 / 100 mg/kg BID
Concentration (mg/L)
Time (hr)
0
250
500
750
1000
0
100
200
300

Figure A5C



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159 Figure A5D

160 Figure A5: Individual fits obtained with the enzyme inhibition pharmacokinetic model for study 1A (A), study 2A (B), study 1B (C) and study
161 2B (D). Loading dose on day 1 and maintenance dose are annotated for each cynomolgus macaque. Dots represent observations, solid line model
162 predictions. Red dots stand for observation below the limit of quantitation.

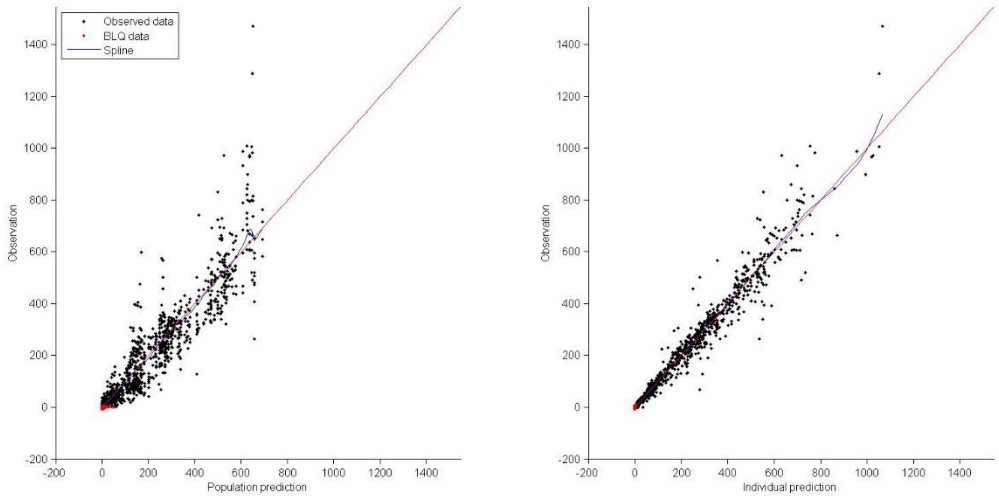


Figure A6: Observations vs population (left) and individual (right) predictions of final PK model. Red dots correspond to residuals of observations below the limit of quantitation.

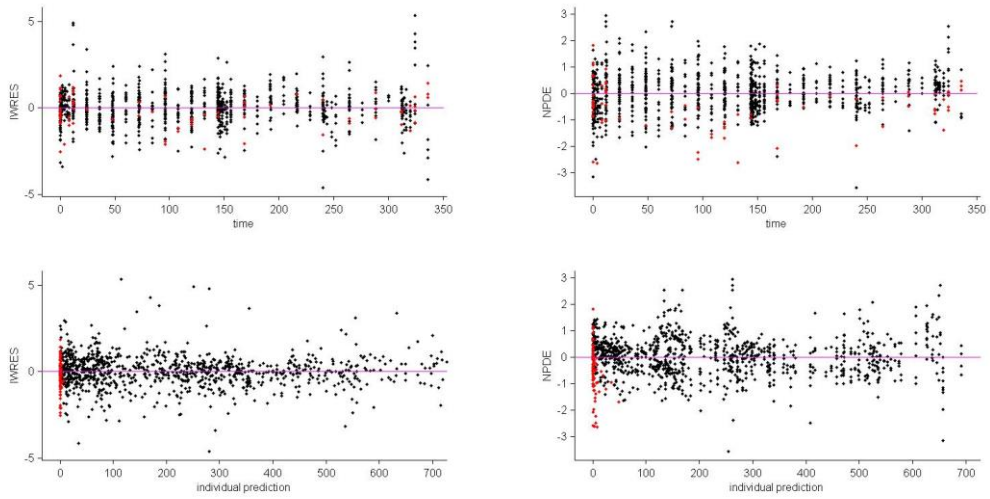
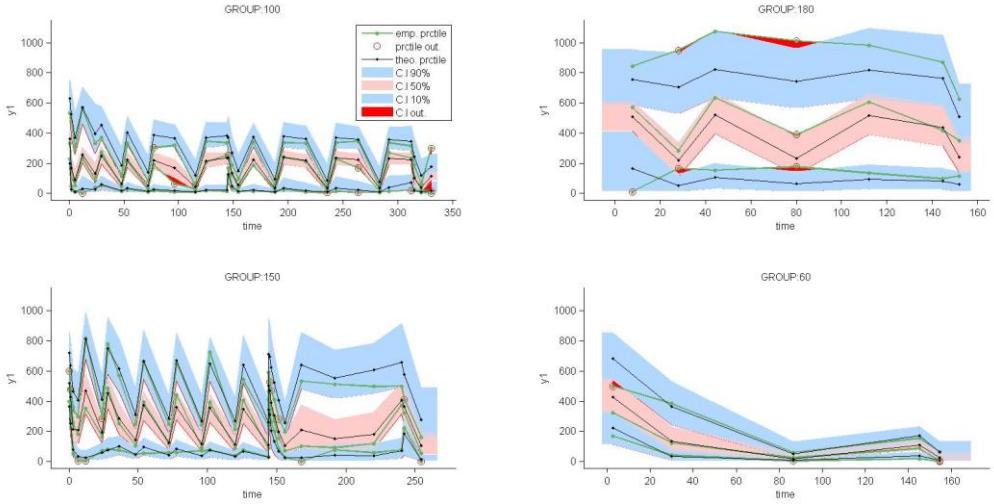


Figure A7: Individual weighted residuals (left) and npde (right) plotted vs time (top line) and vs individual predictions (bottom line) of final PK model. Red dots correspond to residuals of observations below the limit of quantitation.



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176 Figure A8: Visual predictive checks of the final PK model, stratified on maintenance doses.

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